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21 CFR Part 882

Neurological Devices; Effective Date of Requirement for Premarket Approval; Implanted Intracerebral/Subcortical Stimulator for Pain Relief; Final Rule

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. 85M-0056]

Neurological Devices; Effective Date of Requirement for Premarket Approval; Implanted Intracerebral/Subcortical Stimulator for Pain Relief

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to require the filing of an application for premarket approval (PMA) or a notice of completion of a product development protocol (PDP) for the implanted intracerebral/subcortical stimulator for pain relief, a generic type of medical device. After the effective date, commercial distribution of this device must cease, unless a manufacturer or importer has filed with FDA a PMA or a notice of completion of a PDP for its version of the implanted intracerebral/subcortical stimulator for pain relief. The requirement of premarket approval does not compel explantation (surgical removal) of previously implanted devices, whether or not the manufacturer or importer files a PMA or PDP. A decision on whether to recommend explantation of an already-implanted intracerebral/subcortical stimulator for pain relief should be made on an individual basis, depending on whether that course of action is necessary to protect an individual patient's health. This action is being taken under the Medical Device Amendments of 1976.

EFFECTIVE DATE: March 1, 1989.

FOR FURTHER INFORMATION CONTACT: Robert F. Munzner, Center for Devices and Radiological Health (HFZ-430), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7226.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 4, 1979 ((44 FR 51772), FDA published a final rule (21 CFR 882.5840) classifying into class III (premarket approval) the implanted intracerebral/subcortical stimulator for pain relief, a medical device. Section 882.5840 applies to (1) any implanted intracerebral/subcortical stimulator for pain relief that was in commercial distribution before May 28, 1976, the date of enactment of the Medical Devices Amendments of 1976 (the amendments) (Pub. L. 94-295), and (2) any device that FDA has found to be substantially equivalent to the implanted intracerebral/subcortical stimulator for pain relief and that has been marketed on or after May 28, 1976. For the sake of convenience, both the devices that were on the market before May 28, 1976, and the substantially equivalent devices that were marketed on or after that date are referred to as "preamendments devices."

In the **Federal Register** of July 25, 1985 (50 FR 30277), FDA published a proposed rule to require the filing under section 515(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e(b)) of a PMA or a notice of completion of a PDP for the implanted intracerebral/subcortical stimulator for pain relief. In accordance with section 515(b)(2)(A) of the act, FDA included in the preamble to the proposal the agency's proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the premarket approval requirements of the act, and the benefits to the public from use of the device (50 FR 30278). The preamble to the proposal also provided an opportunity for interested persons to submit comments on the proposed rule and the agency's proposed findings. Under section 515(b)(2)(B) of the act, FDA also provided an opportunity for interested persons to request a change in the classification of the device based on new information relevant to its classification. Any petition requesting a change in the classification of the implanted intracerebral/subcortical stimulator for pain relief was required to be submitted by August 9, 1985. The comment period closed on September 23, 1985.

Although FDA did not receive any petitions requesting a change in the classification of the device, several persons submitted comments relating their clinical experiences with the device. Summaries of these comments and the agency's responses follow:

1. Many comments were concerned that FDA may intend to remove the device from commercial distribution by requiring premarket approval. Some persons who submitted comments provided data on the device's safety and effectiveness to persuade FDA to allow its continued distribution.

The agency has not yet made a decision regarding the safety and effectiveness of the generic type of device, the implanted intracerebral/subcortical stimulator for pain relief. (See 21 CFR 860.3(i) for a definition of the term "generic type of device.") The purpose of requiring premarket approval of the device is to obtain the data necessary for FDA to evaluate its safety and effectiveness. FDA believes that safety and effectiveness data are (or should be) readily available to the manufacturers of the device, because the manufacturers have known since the device was classified into class III in 1979 that the device would eventually be subject to the premarket approval requirements in section 515 of the act (21 U.S.C. 360e) and 21 CFR Part 814. Thus, FDA believes that it has given ample notice. FDA believes that much of the data submitted in the comments on the proposal would be useful to manufacturers during their preparation of PMA's for the device.

2. One comment argued that sufficient data currently exist to determine the safety and effectiveness of the device and that further data collection is unnecessary and unduly burdensome.

Because of the kinds of data submitted by the comments on the proposal, FDA agrees that manufacturers of the implanted intracerebral/subcortical stimulator for pain relief may have sufficient data available now and generation of much additional data may not be necessary. Under the amendments enacted by Congress (section 515 of the act) and FDA's implementing regulations, the agency proposed to require that manufacturers submit data on the safety and effectiveness of the device in the form of a PMA as described in 21 CFR Part 814, or submit to FDA a petition requesting reclassification of the device under section 513(e) of the act (21 U.S.C. 360c(e)) and Subpart C of 21 CFR Part 860. Because no petitions requesting reclassification of the device have been received, FDA now is requiring each manufacturer to submit a PMA or cease commercial distribution of the device.

3. Many comments said that the risks to health identified in the proposed regulation (damage to neural tissue, surgical complications, tolerance to stimulation, skin erosion, cerebrospinal fluid leakage, and tissue toxicity) appear exaggerated, as discussed below:

a. The comments said that in the proposed rule FDA had described neural damage and undesirable neurological effects as a result of implantation and use of this device. Several comments stated that little, if any, evidence has been observed of neural damage, either clinically or in histological data. The comments stated that few post-mortem studies have been performed, but in those done, only minimal morphological changes were seen, and those changes observed were considered to be of no greater extent than damage caused by other routine neurological procedures. In addition, comments argued that

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neurological deficits and side effects are rare, and the comments concluded that these risks to health generally resulted from improper placement of electrodes or overstimulation. The comments stated that new designs for electrodes and the development of more precise placement sites, techniques, and stimulation parameters have alleviated most risks of neural damage.

FDA agrees that neural damage and neurological deficits may be infrequent occurrences. In the proposed rule, FDA presented sufficient data to establish that some neural risks to health are associated with the use of this device. The discussion of risks to health presented in the proposed regulation omits any conclusion with regard to these risks. FDA intended to identify the risks that might be eliminated or reduced by requiring premarket approval. FDA also recognizes that improvements may have been made in some of the electrodes used. However, FDA believes that it must perform a detailed analysis of the data on the risks to health from use of the device to provide reasonable assurance of its safety and effectiveness.

b. Several comments believe that FDA's proposed rule exaggerated the risks to health of intraventricular hemorrhage and infection which can result from the implantation procedure. According to studies cited by the comments, infection occurs in a very small percentage of patients; and in these few cases, infection is easily treated with antibiotics or by explanation of the device. The comments stated that the risk of infection is the same or less than from use of similar stereotaxic techniques. The comments also regard the incidence of hemorrhage caused by implantation to be rare, and suggest that the risk is also no more than that involved in similar stereotaxic procedures.

FDA agrees that the incidence of hemorrhage and infection may be infrequent. The proposed rule cites the occurrence of these complications as potentially serious adverse effects associated with the use of this device. The agency believes that regulation of the intracerebral/subcortical stimulator for pain relief through premarket approval is appropriate to assure that these risks are minimized.

c. Some comments asserted that electrode migration is a former problem attributable to poor electrode design and to difficulty in securing the wires to the skull. The comments also asserted that improved electrode design and use of a new burr hole cover and locking component have alleviated the electrode migration problem.

FDA recognizes that new electrode designs and new surgical methods may have reduced the incidence of electrode migration. However, FDA believes that these innovations must be evaluated carefully to determine their impact on the safety and effectiveness of each manufacturer's device.

d. The development of tolerance to electrical stimulation was discussed by several comments. The comments agreed with data cited in the proposed rule which indicated that patients' development of tolerance to electrical stimulation may be the reason that the device becomes ineffective in about 30 percent of patients in whom it is implanted. However, most of the comments disagreed with the data cited in the proposed rule which indicated that a patient who develops tolerance to electrical stimulation frequently also develops tolerance to pain-relieving drugs. The comments also said that, in many cases, the electrical tolerance can be treated through administration of certain drugs.

FDA recognizes that tolerance to stimulation has been reported in 30 percent of the patients treated with the implanted intracerebral/subcortical stimulator for pain relief. These data, along with other data on effectiveness, will be considered by FDA during its review of any PMA's submitted for the device.

e. Several comments discussed the risk to health of cerebrospinal fluid leakage. The comments noted that the studies cited in the proposed rule that pertained to CSF leakage were studies of cerebellar stimulation using the implanted cerebellar stimulator (21 CFR 882.5820). The comments noted that the implant procedure for the cerebellar stimulator involves an open craniotomy as opposed to the burr hole implant procedure used for the intracerebral/subcortical stimulator for pain relief. Therefore, the comments said, the data from these cited studies do not provide an accurate assessment of the risk of cerebrospinal fluid leakage associated with the latter device.

FDA recognizes that the level of risk to health of cerebrospinal fluid leakage associated with use of the intracerebral/subcortical stimulator for pain relief may be lower than the level of risk of cerebrospinal fluid leakage associated with use of the implanted cerebellar stimulator. However, FDA believes that these two devices are sufficiently similar to suggest that a potential risk of cerebrospinal fluid leakage may result from use of the implanted intracerebral/subcortical stimulator for pain relief and that premarket approval is necessary to minimize this risk to health.

FDA advises that the agency has already promulgated a rule requiring any manufacturer of the implanted cerebellar stimulator to submit a PMA for the device or cease commercial distribution (49 FR 26574; June 28, 1984).

f. Several comments said that skin erosion occurs infrequently and that skin erosion was caused by bulky electrode connectors. The comments said that the design of these connectors have been modified to reduce their bulk.

FDA recognizes that manufacturers have made improvements in the design of the electrode connectors which may reduce the risk of skin erosion. However, FDA believes that it should review these data in the form of a PMA to provide reasonable assurance of the safety and effectiveness of this device.

4. Many comments said that in the proposed regulation FDA understated the benefits that can be derived from use of the implanted intracerebral/subcortical stimulator for pain relief. The comments said that use of this device has improved the quality of life for many patients who otherwise are often addicted to drugs, or become suicidal. The comments stated that use of this device for pain relief is a reversible therapy, as opposed to other surgical and ablative techniques. Many comments said that site selection for implantation of the electrodes to treat specific types of pain has become more accurately defined, making patient selection easier and, thus, making use of the device more effective.

FDA recognizes that there are reports of patients who have achieved relief of pain through the use of this device, and also that improvements are being made with respect to the site of electrode implantation and patient selection. However, FDA believes that the degree of benefit offered by this device must be carefully and accurately defined by analysis of all relevant data. Data in the proposed rule indentified some of the benefits found in the scientific literature and also identified some areas where FDA believes that more data need to be studied to assure the safety and effectiveness of these devices.

FDA has reexamined its proposed findings with respect to the degree of risk of illness of injury designed to be eliminated or reduced by requiring the implanted intracerebral/subcortical stimulator for pain relief to meet the statute's approval requirements. The agency concludes that its proposed findings and its conclusion discussed in the preamble to the proposed rule are appropriate. Accordingly, FDA is promulgating a final rule requiring premarket approval of the implanted

intracerebral/subcortical stimulator for pain relief under section 515(b)(3) of the act and is summarizing its findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring that the implanted intracerebral/subcortical stimulator for pain relief have an approved PMA or declared completed PDP, and with respect to the benefits to the public from the use of the device.

I. Findings With Respect to Risks and Benefits

A. Degree of Risk

1. *Damage to neural tissue.* The electrical current used for stimulation and the presence of the electrode may cause injury to brain tissue. Charge densities used to treat patients cannot be determined from published reports of clinical studies. Animal studies indicate that by using low charge densities, electrical injury to brain tissue can be minimized. One study concluded that the upper limit for safe stimulation is 0.05 watt per square inch when biphasic electrical pulses are used. Another study concluded that some neural damage is consistently produced if the charge per phase of the stimulus pulse is 0.45 microculomb or greater. Still another study revealed that neural damage in the cerebral cortex of cats increased proportionally as the charge density per phase increased over the range of 40 to 400 microcoulombs per square centimeter per phase. Several undesirable neurological effects, including coagulated brain tissue, blurring of vision, lesions in the target points, vertigo, focal and motor seizures, and emotional changes have been reported in patients treated with deep brain stimulation.

2. *Surgical complications.* Complications may occur because of the surgical implantation procedures. Because the surgical procedures involve the brain, complications such as punctured blood vessels, intraventricular hemorrhage, and infections are usually serious. One reported death has occurred due to infection.

3. *Electrode migration.* Implanted electrodes can spontaneously move from their original position or they can be dislodged. Electrode movement may cause damage to brain tissue or produce stimulation in an area of the brain which may result is undesirable neurological effects. Electrode migration has been reported in 2 to 17 percent of patients.

4. *Tolerance.* Tolerance to stimulation may develop and has been reported to occur in 30 percent of patients in whom the device is implanted. Patients who have become tolerant to deep brain stimulation may also demonstrate tolerance to some pharmacological opiates. If such tolerance occurs, the patient would not be able to obtain relief of pain with electrical stimulation or with narcotic analgesics.

5. *Skin erosion.* Erosion of the skin can occur in the scalp over the area where the electrodes exit from the cranium or can occur over the site of the receiver. Erosion of the device through the scalp may be the most troublesome source of infection and may necessitate the explanation of the device.

6. *Cerebrospinal fluid leakage.* Cerebrospinal fluid leakage is a risk common to devices implanted in the central nervous system. When this occurs, reoperation is required to correct the condition.

7. *Tissue toxicity.* Although the surface materials used in the implanted receiver, lead wires, or electrodes are generally believed to be biocompatible, it is possible that contaminants may be introduced into the materials used in the device during its manufacture, causing adverse tissue reactions.

Considering the risks and probable benefits associated with the implanted intracerebral/subcortical stimulator for pain relief, FDA concludes that the device should undergo premarket approval to establish conditions for use that will minimize risks and determine whether the risks of using the device are balanced by benefits to patients.

B. Benefits of the Device

The benefits of the implanted intracerebral/subcortical stimulator for pain relief to patients are questionable. Published reports indicate that the device may provide pain relief for selected patients, but may not be suitable for treating certain patients or all types of pain.

The implanted intracerebral/subcortical stimulator for pain relief has been reported to provide relief from peripheral chronic pain syndrome resulting from carcinomas, failed low backs, nerve entrapments, and phantom limb syndromes. Some investigators have reported successful treatment of pain of central origin, e.g., thalmic syndromes, brain stem infarction, and spinal cord injury. Other investigators have concluded that the device is probably not beneficial in treating central pain. Electrical stimulation of both the periaqueductal gray and periventricular gray matter appears to produce opiate-mediated analgesia; stimulation in these areas may produce unpleasant or intolerable side effects. Other researchers have reported pain relief with stimulation within the internal capsule, although there is not any indication that endogenous opiates are produced when this area is stimulated. Additional data are required to explain the variable clinical results obtained to date with the device.

II. Final Rule

Under section 515(b)(3) of the act, FDA is adopting the proposed findings as published in the preamble to the proposed rule and is issuing this final rule to require premarket approval of the generic type of device, the implanted intracerebral/subcortical stimulator for pain relief, by revising paragraph (c) in § 882.5840.

Under the final rule, a PMA or a notice of completion of a PDP is required to be filed on or before March 1, 1989, for any implanted intracerebral/subcortical stimulator for pain relief that was in commercial distribution before May 28, 1976, or that has been found by FDA to be substantially equivalent to such a device on or before March 1, 1989. An approved PMA or a declared completed PDP is required to be in effect for any such device on or before August 28, 1989. (If FDA finds that continued availability of an implanted intracerebral/subcortical stimulator for pain relief for which a PMA has been timely filed is necessary for the public health, FDA may, under section 515(d)(1)(B)(i) of the act, extend the 180-day period for taking action on the PMA.) Any implanted intracerebral/subcortical stimulator for pain relief that was not in commercial distribution before May 28, 1976, or that has not on or before March 1, 1989, been found by FDA to be substantially equivalent to an implanted intracerebral/subcortical stimulator for pain relief that was in commercial distribution before May 28, 1976, is required to have an approved PMA or a declared completed PDP in effect before it may be marketed.

If a PMA or a notice of completion of PDP for an implanted intracerebral/subcortical stimulator for pain relief is not filed on or before March 1, 1989, that device will be deemed adulterated under section 501(f)(1)(A) of the act (21 U.S.C. 351(f)(1)(A)), and commercial distribution of the device will be required to cease. The device may, however, be distributed for investigational use, if the requirements of the investigational device exemption (IDE) regulations (21 CFR Part 812) are met.

Under § 812.2(d) of the IDE regulations, FDA hereby stipulates that the exemptions from the IDE requirements in § 812.2(c) (1) and (2) will no longer apply to clinical investigations

of the implanted intracerebral/subcortical stimulators for pain relief. Further, FDA concludes that investigational implanted intracerebral/subcortical stimulators for pain relief are significant risk devices as defined in § 812.3(m), and advises that as of the effective date of § 882.5840(c) the requirements of the IDE regulations regarding significant risk devices will apply to any clinical investigation of an implanted intracerebral/subcortical stimulator for pain relief. For any such device, therefore, an IDE submitted to FDA, under § 812.20, is required to be in effect under § 812.30 before an investigation is initiated or continued on or after March 1, 1989. FDA advises all persons who intend to sponsor any clinical investigation involving the implanted intracerebral/subcortical stimulator for pain relief to submit an IDE application to FDA no later than January 30, 1989, to avoid the interruption of ongoing investigations.

As discussed at length in paragraph 1 of the preamble to the final PMA rule (51 FR 26342, 26343; July 22, 1986), FDA will not request recall, or recommend seizure, of an implanted device under circumstances that would necessitate explantation of the device to effect recall or seizure unless such action is necessary to protect the health of the patient. If an implanted device is adulterated under section 501(f)(1)(A) of the act because of the manufacturer's failure to submit a PMA and explantation of the device is not necessary to protect the health of the patient, FDA will require only that commercial distribution of the device cease. FDA also may invoke its authorities under section 518 of the act (21 U.S.C. 360h) to require notification, repair, replacement, or refund when a device in commercial distribution presents an unreasonable risk of substantial harm to the public health.

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) and (e)(4) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Economic Impact

FDA has examined the economic consequences of this final rule in accordance with the criteria in section 1(b) of Executive Order 12291 and found that the rule will not be a major rule as specified in the Order. The agency believes that only three small firms will be affected by this rule. Therefore, the agency certifies under the Regulatory Flexibility Act (Pub. L. 96-354) that the rule will not have a significant economic impact on a substantial number of small entities. An assessment of the economic impact of this final rule has been placed on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 882

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 882 is amended as follows:

PART 882—NEUROLOGICAL DEVICES

1. The authority citation for 21 CFR Part 882 continues to read as follows:

Authority: Sec. 501(f), 510, 513, 515, 520, 701(a), 52 Stat. 1055, 76 Stat. 794–795 as amended, 90 Stat. 540–546, 552–559, 565–574, 576–577 (21 U.S.C. 351(f), 360, 360c, 360e, 360j, 371(a)); 21 CFR 5.10.

2. Section 882.5840 is amended by revising paragraph (c) to read as follows:

§ 882.5840 Implanted intracerebral/subcortical stimulator for pain relief.

* * * * *

(c) *Date premarket approval application (PMA) or notice of completion of a product development protocol (PDP) is required.* A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before March 1, 1989, for any implanted intracerebral/subcortical stimulator for pain relief that was in commercial distribution before May 28, 1976, or that has on or before March 1, 1989, been found to be substantially equivalent to an implanted intracerebral/subcortical stimulator for pain relief that was in commercial distribution before May 28, 1976. Any other implanted intracerebral/subcortical stimulator for pain relief shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.

Dated: October 11, 1988.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

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